REMARKS/ARGUMENTS

Reconsideration of this application is requested.

Claims 1-8, 17-19, 25-27, and 30 are allowed. Claims 9-16, 20-24, 28 and 29 are rejected according to the Office Action Summary. However, no reason is stated in the Office action for the rejection of either claim 21 or 28. Applicant assumes that the Examiner intended to reject claims 21 and 28 for the same reasons given with respect to claims 20, 22-24 and 29, as set forth on page 3 of the Office action.

The applicant does not understand the rejection of claims 9-16 as "unpatentable over the arcadi [sic] reference (1986) and arcadi [sic] reference (1990)". It is true that the 1986 Arcadi reference disclose the use of a saline suspension of Rhodamine-123 in animal experiments. However, as conceded in the Office action, the Arcadi "references do not teach applicant's specific carriers set forth in the instant claims". The Office action on page 2 then states that:

> ". . . accordingly, one skilled in this art would find ample motivation from the prior art supra to make a pharmaceutical composition of the prior art rhodamine-123 anticancer agent with a reasonable expectation that said composition would be effective for treating cancer in the absence of a side-by-side comparison over the prior art pharmaceutical composition."

The preceding rejection is misplaced for at least two reasons. First, nothing in either of the Arcadi references provides any "motivation" or "reasonable expectation" that the applicant's composition would be effective in prolonging human

life of carcinoma patients. As is clear from the declarations of Dr. Jones (of record in the prosecution of this application), the drug industry and the medical profession have spent millions of dollars and thousands of research hours seeking an effective therapy for treating prostate cancer, which kills thousands of men annually. If the Arcadi references of 1986 and 1990 had actually created a reasonable expectation that treatment with Rhodamine-123 would prolong the life of prostate cancer victims, that compound would have been put to wide use using the applicant's composition defined by claims 9-16. Instead, Rhodamine-123 was dismissed as clinically inadequate by other workers in that field. Second, the rejection referred to above appears to require that the applicant run clinical experiments (that is, tests on human patients) with a saline suspension of Rhodamine-123 (which Dr. Arcadi's declaration of February 13, 1997 states would be unacceptable for treating patients because the suspension would result in uncertain dosage, and there would be an unknown amount of solubilizing of the Rhodamine-123). Such experiments would be not only dangerous and expensive, but they would in no way demonstrate whether or not applicant's claimed composition is obvious in view of the cited references. That determination is easily made by examining the references to see if they provide motivation to make the claimed composition with a reasonable expectation that it would be effective in prolonging human life. Nothing in either of the two references supports that contention. The March 17, 2003 Jones declaration (quoted in part below) makes it clear that:

> . . . even though a drug may be demonstrated to have anticarcinoma activity in laboratory *in vitro* and animal experiments, that does not justify a "reasonable expectation" that it will be effective in treating human carcinoma.

Claims 20, 22-24 and 29 were rejected "as being unpatentable over the Bernal et al., reference of record as set forth in paper no. 14." There are two Bernal et al. references of record. Applicant believes that the reference relied on in the Office action is the one appearing in *Science (1983), 222 (4620), 160-72.* The Office action apparently quotes an excerpt from lines 1 and 2 of the Abstract of that reference by stating "The Bernal et al. reference teaches Rhodamine-123 'exhibited anti-carcinoma activity in mice with various exptl. Carcinomas…'" Applicant cannot find this exact excerpt in either of the Bernal et al. references, but agrees that the 1983 Bernal et al reference states in the Abstract that "Rhodamine-123 exhibited anti-carcinoma activity in mice". However, the Office action (on Page 3) concedes that "The Jones declaration refers to the Bernal et al. reference does not disclose that human life can be prolonged by treating victims of carcinoma with rhodamine-123, this is true but the instant claims are <u>not</u> directed to 'prolonging human life'". Claims 20-24, 28 and 29 have been amended to make it clear that the claims are now directed to prolonging human life.

The Office action also states on page 3 that "The declaration refers to Exhibits B and C, these references are directed to <u>in vitro</u> data only while the instant reference is

directed to in vivo use." This statement overlooks paragraph 3 of the Jones declaration (of March 17, 2003) which states:

> 3. I am familiar with the Office actions dated 3/11/2002 and 10/31/2002, which rejected claims 20-24 and 28 as unpatentable over the Bernal et al. reference, which states (in the Abstract) "Rhodamine-123 exhibited anticarcinoma activity in mice" (published 14 October 1983 in *Science*, Vol.222, pp. 169-172).

Moreover, the Jones declaration clearly refers to both *in vitro* and *in vivo* experiments. For example, the Jones declaration on pages 2 and 3 states:

> 6. Over the past 50 years, hundreds of drugs tested *in vitro* and in laboratory animals have shown potential as antitumor agents, but subsequently failed in clinical tests, or never reached that stage. For example, see U.S. Patent 5,360,803 (filed November 6, 1992, and assigned to Dan Farber Cancer Institute and Fuji Photo Film Co., Ltd.), which discloses at least 348 antitumor agents for possible treatment of prostate cancer in humans. I review regularly publications and reports dealing with agents for treating prostate cancer and many other forms of carcinoma. As far as I am aware, none of those disclosed by that patent have been accepted by the medical profession as a treatment for prolonging life of patients afflicted with hormone-refractory prostate cancer.
>
> 7. Contrary to the statement in the 03/11/2002 and 10/31/2002 Office actions, the 1983 Bernal et al. reference referred to in paragraph 3 above would not cause one of ordinary skill in this work to reasonably expect that Rhodamine-123 would be any more effective in combating carcinoma than any of many other drugs which have been tested *in vitro* and in laboratory

animals with promising results, but which have failed to produce any therapeutic effects in human patients. Nothing in the Bernal et al. reference discloses that human life can be prolonged by treating victims of carcinoma with Rhodamine-123.

8. An important problem in the management of carcinoma is the heterogeneity of the disease. For example, unequivocal evidence from animal studies, from the growth of human prostate cancer in tissue culture, in the xenograft system, and from human biopsy material shows that many different types of tumor cells exist within prostate cancer, and in many other forms of carcinoma. Accordingly, even though a drug may be demonstrated to have anticarcinoma activity in laboratory *in vitro* and animal experiments, that does not justify a "reasonable expectation" that it will be effective in treating human carcinoma. This is well recognized by skilled workers in this field. For example, attached to this Declaration as Exhibit A is a paper by the inventor and others (including me) entitled "Studies of Rhodamine-123: Effect on Rat Prostate Cancer and Human Prostate Cancer Cells *In Vitro*," presented in the *Journal of Surgical Oncology* 59:86-93 (1995), which describes some experimental work providing some basis for this patent application. Under "Editorial Comments" at the end of the paper, Dr. T. Vincent Shankey, with the Departments of Urology and Pathology at Loyola University Medical Center in Maywood, Illinois, rejects the work described in the paper as supporting "the thesis that Rh-123 may be an effective agent for the treatment of metastatic hormone-refractory prostate cancer" because it "is a connection that has too often failed in the past." Dr. Shankey's criticism cites other authorities who have pointed out that "the local environment of solid malignancies *in situ* has a profound impact on the responsiveness or nonresponsiveness of cancers where they really count to a patient in his or her body."

In the above-quoted paragraphs from the Jones Declaration, reference is made to drugs tested *in vitro* and in laboratory animals (*in vivo*). Accordingly, the apparent objection to the Jones declaration on the grounds that it deals with "in vitro data only" should be withdrawn.

This application is now in condition for allowance, and such action at an early date is requested.

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By R. W. Johnston

R. William Johnston
Reg. No. 17,968
626/795-9900

RWJ/cam
CLS PAS529498.1-*-10/6/03 10:45 AM